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Applicant : Parent et al.
Serial No. : 10/611,439
Filed : July 1, 2003
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Attorney's Docket No.: 00986-084001 / 5099

Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 21 with the following amended paragraph:

Conjugation of polyethylene glycol ("PEG") and certain biological polymers and enzymes including insulin and catalase are disclosed in U.S. Pat. No. 4,179,337. U.S. Pat. Nos. 5,539,063 and 6,042,822 disclose respectively, (a) methods of conjugation of PEG using so-called "unique linkers" to improve the attachment and activity of the conjugates; and (b) active conjugates of .alpha.-interferon to PEG. U.S. Pat. No. 5,366,958 discloses the attachment of biologically active agents to fibronectin using N-hydroxysuccinimide; and International Patent No. WO 0,078,365 teaches oxidizing hyaluronans to form aldehyde groups reactive with diamines or amino polyalkylene glycols which are then reacted with oxidized sulfated polysaccharides. In U.S. Pat. Nos. 4,582,865 and 4,605,681, the preparation of cross-linked hyaluronan through vinyl sulfone linkages, as well as the attachment of these materials to the matrix of an insoluble gel - via ether linkages are described.

Prestwich, Glenn D., in "Biomaterials from Chemically-Modified Hyaluronan, Glycoforum (Mar. 29, 2001) suggests that drugs may be conjugated with hyaluronan. Finally, Cirino, et al., Carbohydrate Research (1971), 17(1), 67-68 teaches that, in addition to simple cross-links (a) and simple substitutions (b), divinyl sulfone can also react with carbohydrates (e.g., cellulose, D-glucose) leading to complex modification of the carbohydrate:

(a) ~~RO-CH₂-CH₂-SO₂-CH₂-CH₂-OR~~ OR ~~RO-CH₂-CH₂-SO₂-CH₂-CH₂-OR~~; and (b) ~~RO-CH₂-CH₂-SO₂-CH=RO-CH₂-CH₂-SO₂-CH=CH₂~~, wherein R is a carbohydrate.

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Please replace the paragraph beginning at page 3, line 6 with the following amended paragraph:

The conjugate is the reaction product of the above-described intermediate which has the general formula $P-O-CH_2-CH_2-SO_2-(CH=CH_2)_n$, $P-O-(CH_2-CH_2-SO_2-CH=CH_2)_n$, wherein n is an integer and is at least 1, P represents a hydrophilic biopolymer, and in a preferred embodiment, the biopolymer (P) is a hyaluronan or a hylan and a biologically active material capable of being covalently and nucleophilically bonded to said intermediate. The intermediate may also contain, in addition to the free, or reactive vinyl groups, some extent of DVS cross-linking.

Please replace the paragraph beginning at page 3, line 13 with the following amended paragraph:

In still a further embodiment, the invention provides, in addition to the simple cross-links and substitutions described by Cirino, et al., the preparation of DVS+carbohydrate (e.g., cellulose, D-glucose, etc.) complexes of the formula: $RO-CH_2-CH_2-SO_2-CH_2-CH_2-O-(CH_2-CH_2-SO_2-CH_2-CH_2-O)_n-CH_2-CH_2-SO_2-CH=$ $RO-CH_2-CH_2-SO_2-CH_2-CH_2-O-(CH_2-CH_2-SO_2-CH_2-CH_2-O)_n-CH_2-CH_2-SO_2-CH=CH_2$, wherein R is a carbohydrate and n is 0, 1, 2, 3, . . . , which complex is then reacted with R'OH, wherein R' is a drug molecule, water, a protein or an additional carbohydrate to form: $RO-CH_2-CH_2-SO_2-CH_2-CH_2-O-(CH_2-CH_2-SO_2-CH_2-CH_2-O)_n-CH_2-CH_2-SO_2-CH_2-CH_2-OR'$, wherein $RO-CH_2-CH_2-SO_2-CH_2-CH_2-O-(CH_2-CH_2-SO_2-CH_2-CH_2-O)_n-CH_2-CH_2-SO_2-CH_2-CH_2-OR'$, wherein n is 0, 1, 2, 3, . . . The foregoing reaction path shows how the complex and the drug carbohydrate complex are formed. The advantage of this kind of modification is that the drug is conjugated to the carbohydrate carrier with a longer linking arm, as a result of which, the intermediate may be more reactive to conjugating a drug.

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Please replace the paragraph beginning at page 4, line 14 with the following amended paragraph:

The intermediate has the general formula $\text{P-O-CH}_2\text{-CH}_2\text{-SO}_2\text{-(CH=CH}_2\text{)}_n\text{-P-O-(CH}_2\text{-CH}_2\text{-SO}_2\text{-CH=CH}_2\text{)}_m$, wherein n is an integer and is at least 1, P represents a hydrophilic biopolymer having a functional groups capable of reacting with divinyl sulfone.